

REVIEW ARTICLE

Surgical Management of Adrenal Metastases From Lung Cancer

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Background and Objectives: Adrenal metastases from lung cancer usually indicate systemic disease and incurability. However, a small subset of patients with isolated adrenal metastases may achieve long-term survival with aggressive surgical resection of the adrenal gland. To clarify the role of adrenalectomy for metastatic lung cancer, we undertook a review of the published literature on this topic.

Methods: The English-language medical literature was searched for papers reporting surgical resection of adrenal metastases from lung cancer. Eleven articles were retrieved and their data pooled for analysis.

Results: Sixty patients (including seven previously reported from our institution) formed the basis of this collective review. Thirty-two patients pooled from small series and case reports had a median survival of 24 months, and approximately one-third were 5-year survivors. Twenty-eight patients reported in two large series had a less favorable survival (approximately 14 months median survival).

Conclusions: Surgical resection of isolated adrenal metastases from lung cancer appears to have a modest survival advantage over nonoperative therapy, and it occasionally results in long-term survival. However, the relatively encouraging survival results reported in the literature could be related to careful patient selection for this aggressive therapy, publication bias in favor of positive treatment outcomes, or a combination of the two. Nevertheless, the results are encouraging enough to justify further investigation of this aggressive treatment strategy. Practical guidelines for management are proposed. *J. Surg. Oncol.* 1998;69:54–57. © 1998 Wiley-Liss, Inc.

KEY WORDS: adrenalectomy; adrenal gland neoplasm surgery; lung cancer; secondary adrenal gland neoplasms; combined antineoplastic agents

INTRODUCTION

Distant metastases from lung cancer usually indicate incurability. Therefore, surgical resection of the primary lung cancer, or metastatic sites, is generally contraindicated for stage IV lung cancer [1]. However, a very small subset of patients with solitary metastases from lung cancer may be curable with aggressive treatment. Surgical resection of solitary brain metastases from lung cancer,

along with resection of the pulmonary tumor, can result in long-term survival [2]. Surgical resection of solitary metastases in other sites, including the adrenal gland, remains controversial [3]. Several small series of adre-

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Accepted 8 June 1998

nalectomy for metastatic lung cancer have been reported [4–14]. This treatment approach may be worthy of further investigation and application, but it is difficult to draw meaningful conclusions based on small series from single institutions. To clarify the role of adrenalectomy for metastatic lung cancer, we undertook a review of the published literature on this topic.

MATERIALS AND METHODS

The English-language medical literature was searched manually and by Medline for papers reporting surgical resection of adrenal metastases from lung cancer. Eleven articles were retrieved and their data form the basis of this review [4–14]. Data pertaining to histology, detection (synchronous or metachronous), location (ipsilateral or contralateral to pulmonary tumor), local-regional stage, and survival were collected and then pooled for analysis. Not all articles gave information on all of these parameters. Finally, possible prognostic factors were sought from articles reporting relatively large patient series.

RESULTS

A total of 60 patients with isolated adrenal metastases from lung cancer were reported in 11 articles. Thirty-two patients were reported in enough detail to permit pooling of data for analysis [4–9,12,14]. The other 28 patients were reported from two institutions, and only summarized data are available for these patients [10,11,13].

In the group of 32 patients pooled from literature reports, there were 22 adenocarcinomas, 6 large cell undifferentiated carcinomas, and 4 squamous cell carcinomas. Synchronous adrenal metastases occurred in 19 patients and the other 13 patients had metachronous adrenal metastases. Time to metachronous adrenal metastases detection ranged from 4 to 33 months, with a median disease-free interval of 11 months. Location of adrenal metastases was ipsilateral in 16, contralateral in 15, and bilateral in 1 patient. Local-regional stage was stage I in 7, stage II in 5, stage IIIa or IIIb in 14, and not specified in 6 patients. Median survival in this group of patients was 24 months, and approximately one-third were 5-year survivors. There were no statistically significant survival differences for the variables examined (histology, time of detection, location, local-regional stage).

Data for the other 28 patients, reported from two institutions, are available in summarized form. One large series of 17 patients with isolated adrenal metastases from lung cancer had a 14-month median survival after adrenalectomy [13]. Median survival for the first eight patients in the series was 31 months [10]. In another large series, 11 lung cancer patients and 41 patients with other primary tumors underwent adrenalectomy for isolated metastases [11]. Survival for the entire group was 40% at

2 years (median survival approximately 13 months). Survival for the lung cancer subgroup was not given, but survival did not significantly differ for the various primary tumors. These three reports from two large institutions show poorer survival than that derived from combining individual case reports from the literature. This is not surprising; case reports traditionally have a publication bias in favor of good treatment outcomes.

It was not possible to identify significant prognostic factors in this collective review of the literature. However, completeness of resection certainly appears to be very important for long-term survival after surgery for isolated adrenal metastases [11,13]. In addition, a long disease-free interval is probably a favorable factor for metachronous tumors [7,13,14]. Completeness of resection and disease-free interval are certainly critical determinants of survival after metastectomy in other organ systems [15].

DISCUSSION

The adrenal gland is a common site for lung cancer metastases. Autopsy studies have shown adrenal metastases in over one-third of patients dying with lung cancer [16]. The vast majority of patients with lung cancer metastatic to the adrenal glands are incurable; they usually have hematogenous spread of disease to other sites. However, a small subset of patients may have isolated hematogenous spread to one adrenal gland. Conceptually, these patients are suitable for aggressive treatment, including resection of the involved adrenal gland. Systemic treatment with chemotherapy is also critical in this setting, as truly isolated hematogenous metastases to extracranial sites is unusual.

Isolated adrenal metastases from lung cancer may not all share the same mechanism of cancer spread. Although most adrenal metastases undoubtedly are a manifestation of hematogenous metastases, some adrenal metastases may develop from lymphatic spread of lung cancer [17]. Lymphatic connections between the lung and the retroperitoneum do exist [18]. One large autopsy study found a relationship between ipsilateral adrenal metastases and limited metastatic disease. Widespread metastatic disease was associated with contralateral or bilateral adrenal metastases [19]. This study supports a lymphatic origin for some of the isolated adrenal metastases seen in lung cancer patients [17,19]. If lymphatic spread to the adrenal glands truly does occur, the metastatic pathophysiology would be more regional than distant in nature. In theory, adrenal metastases of lymphatic origin should be more suitable for aggressive surgical treatment than adrenal metastases arising from hematogenous spread [12]. However, the lymphatic theory of adrenal metastases origin remains speculative and largely unsupported at this time.

In this review, surgical resection of isolated adrenal metastases from lung cancer gave a median survival of

24 months for patients reported in small series, and approximately 14 months for patients reported in larger series. This survival is certainly better than that typically associated with metastatic lung cancer [20], and it appears to be better than that seen with nonoperative treatment of apparently isolated adrenal metastases from lung cancer [8,10]. Nevertheless, the nature of the reports in the literature, including our own [5,12], suggests the possibility of selection bias as an explanation for these relatively favorable survival results. Patients with better performance status and tumor biology were undoubtedly selected for this aggressive surgical approach, while many other patients underwent nonoperative treatment, and went unreported. Notwithstanding this obvious limitation of the published data, the results of surgical resection of isolated adrenal metastases from lung cancer are encouraging enough to justify further investigation of this aggressive treatment strategy.

Although the procedure is "investigational," surgical resection of adrenal metastases from lung cancer is not common enough to be studied by randomized, or even large phase II, trials. Practical guidelines for surgical treatment of apparently isolated adrenal metastases from lung cancer are currently needed. Based on the data reviewed herein, we would propose the following approach to this difficult problem.

The diagnosis of an isolated adrenal metastasis should ideally be confirmed by needle biopsy [21,22]. Many adrenal masses in otherwise operable lung cancer patients prove to be benign adenomas [22]. Although newer imaging modalities, such as magnetic resonance imaging [23] and positron emission tomography [24], are very promising, needle biopsy remains the definitive test of adrenal metastases at this time [21,22].

Patients with synchronous adrenal metastases should undergo complete multisystem radiological staging, and mediastinoscopy, before being considered for resection of the lung tumor and adrenal metastases. The presence of mediastinal lymph node metastases is a predictor of poor survival in this circumstance, and surgical treatment of the primary cancer and adrenal metastasis is not appropriate [14]. If preoperative staging investigations indicate a truly solitary adrenal metastasis, and the patient is fit, resection of the both the primary lung cancer and the involved adrenal gland are indicated. The adrenalectomy can be done at the time of pulmonary resection (through an ipsilateral phrenotomy, or separate abdominal or lumbar approach), or it may be done as a completely independent operative procedure [5,14]. All efforts must be made to obtain a complete surgical resection of the metastatic tumor [11,13]. Occult systemic metastases are the common cause of failure after aggressive surgical treatment of adrenal metastases from lung cancer. Therefore, chemotherapy is indicated, either before or after resection [8,10,12].

Patients with metachronous adrenal metastases require multisystem radiological restaging to rule out other local, regional, or metastatic disease. If an adrenal mass appears within the first year of lung cancer treatment, and imaging studies suggest malignancy, it is reasonable to assume that the lesion is a metastatic deposit without resorting to needle biopsy. Longer disease-free intervals raise the question of coincident development of benign adrenal adenomas, and needle biopsy is preferable. Surgical resection of an isolated metachronous adrenal metastasis is an appropriate therapeutic intervention if the patient is fit enough for the operative procedure [7,13]. Chemotherapy should be given either before or after the adrenalectomy [5,8,10,12].

CONCLUSIONS

Surgical resection for isolated adrenal metastases from lung cancer appears to have a modest survival advantage over nonoperative therapy, and it occasionally results in long-term survival. However, the relatively encouraging survival results reported in the literature could be related to careful patient selection for this aggressive therapy, publication bias in favor of positive treatment outcomes, or a combination of the two. Surgical intervention for lung cancer patients with synchronous or metachronous adrenal metastases cannot be considered "standard" therapy at this time. Favorable results in this group of patients can only be obtained by careful preoperative cancer staging and thoughtful patient selection.

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